Organic Chemistry

Synthesis of stereoisomers of 2,4-diaminoglutaric and 2,5-diaminoadipic acids

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Stereoisomers of 2,4-diaminoglutaric and 2,5-diaminoadipic acids were synthesized from glutamic and 2-aminoadipic acids, respectively. The stereochemistry of the products was established by ^{1}H NMR spectroscopy and X-ray analysis.

Key words: 2,4-diaminoglutaric acid, 2,5-diaminoadipic acid, nucleophilic substitution; stereoisomers; racemization.

2,4-Diaminoglutaric acid (**1a**) has been previously isolated as a natural product[1,2] and synthesized by different methods.[1—4] The (2*S*,4*S*)-enantiomer of **1a** has been synthesized[4] and its complexing properties have been studied.[5] Methods for the synthesis of 2,5-diaminoadipic acid (**1b**)[6,7] and its stereoisomers[8] are also known. It is interesting to note that derivatives of acids **1a,b** exhibit antitumor activity.[9,10]

We have developed simple methods for the synthesis of diastereomers of compounds **1a,b** from the corresponding monoaminodicarboxylic acids, *viz.*, glutamic (**2a**) and 2-aminoadipic (**2b**) acids.

Compound **2a** is readily transformed into methyl 4-bromo-*N*-phthalylglutamate (**3a**).[11] Its reaction with potassium phthalimide (PP) in DMF followed by separation of the mixture of diastereomers afforded methyl 2,4-diphthalimidoglutarates (*threo*-**4a** and *meso*-**4a**), whose acid hydrolysis resulted in *threo*- and *meso*-**1a** diastereomers (Scheme 1).

An attempt to obtain the *threo*-form of **4a** from *erythro*-**3a** was unsuccessful, since the reaction of the latter with PP in DMF was accompanied by racemization. Stirring of an equimolar mixture of *meso*-**4a** and PP in DMF for 3 h at ~ 20 °C resulted in a mixture of diastereomers of **4a** (*meso*/*threo* = 5 according to HPLC data). Evidently, PP is a very strong base, since the inversion of the carbanion follows the abstraction of the α-proton. The alternative mechanism of racemization of the phthalimide group involving nucleophilic substitution by the phthalimide ion is impossible, since heating of an equimolar mixture of *meso*-**4a** and potassium 4-nitrophthalimide in DMF for 6 h at 68 °C did not afford (HPLC) diastereomers of methyl 2-phthalimido-4-(4-nitrophthalimido)glutarate (**5**),

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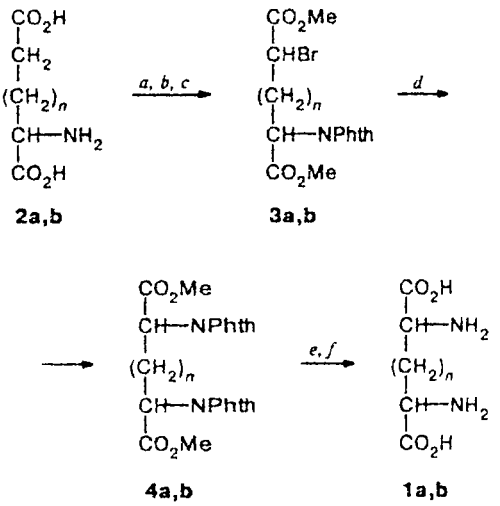
Scheme 1



Phth = phthaloyl
1—4: n = 1 (**a**), 2 (**b**)

Reagents: *a*. MeOCONPhth; *b*. Br_2, PBr_5; *c*. MeOH; *d*. KNPhth; *e*. HCl (**a**), KOH, HCl (**b**); *f*. C_5H_5N.

which were synthesized independently and used as standards.

The nucleophilic substitution of the halogen atom in compound **3a**, similarly to the reaction with aromatic amines,[12] is accompanied by Walden inversion. For example, bromide **3a** containing 66% of the *threo*-isomer afforded a diastereomeric mixture of **4a** with a *meso/threo* ratio of 1.56. When this reaction mixture was kept for 3 days at ~ 20 °C, an equilibrium mixture of diastereomers of **4a** (*threo/meso* = 2.7) was formed. One or the other method for the synthesis can be chosen, depending on the type of the diastereomer required. The *meso*- and *threo*-diastereomers of **4a** were isolated by chromatography; acid hydrolysis of these isomers followed by treatment with pyridine resulted in the *meso*- and *threo*-diastereomers of 2,4-diaminoglutaric acid (**1a**).

The structure of compounds obtained was confirmed by elemental analyses and spectral methods. The configurations of the diastereomers of compounds **4a** and **1a** were determined on the basis of the differences in the ^{1}H NMR spectra due to the different symmetry types of the *threo*- and *meso*-isomers.[13] For example, the methylene and methine protons in *threo*-isomers of **4a** and **1a** are mutually chemically equivalent. Therefore, their spin system is of the AA′XX′ type, which degenerates into two doublets of doublets in the spectrum of *threo*-**4a** or two triplets for *threo*-**1a** typical of the A_2X_2 system. On the contrary, the methine protons in *meso*-isomers **4a** and **1a** are magnetically and chemically equivalent, whereas the methylene protons are diastereotopic. Therefore, an ABX_2 spin system is observed in the ^{1}H NMR spectra of *meso*-isomers **4a** and **1a**.

Methyl 5-bromo-2-phthalimidoadipate (**3b**) was obtained similarly to compound **3a** [11] by bromination of 2-phthalimidoadipic acid (**2b**). However, unlike the case with its analog **3a**, we were unable to find conditions for the separation of the diastereomers. The reaction of compound **3b** with PP in DMF at 20 °C followed by chromatographic purification afforded a mixture of diastereomers of methyl 2,5-diphthalimidoadipate (**4b**) (*cf.* Ref. 6). The *meso*-form of **4b** was isolated in low yield by crystallization from ethanol. The conditions for the separation of *threo*- and *meso*-isomers of **4b** by HPLC were also found. The removal of the protective groups of **4b** was carried out in two steps by alkaline hydrolysis followed by acid hydrolysis, as described earlier.[6]

The configuration of *meso*-**4b** was unambiguously established by X-ray structural analysis. Its molecular structure is shown in Fig. 1. The atomic coordinates are given in Table 1, and the bond lengths and the main bond angles are given in Tables 2 and 3. The carbon skeleton of the molecule has a zigzag *trans-trans-trans* configuration. The C(1)—C(2)—C(3)—C(4) and C(2)—C(3)—C(4)—C(5) torsion angles are 168.8° and 180°,

Table 1. Coordinates of the basis atoms with standard deviations (×10^4) in the molecule of *meso*-**4b**

Atoms	*x*	*y*	*z*
O(1)	8219(3)	9411(3)	4438(2)
O(2)	7927(2)	8911(2)	6862(2)
O(5)	5582(2)	6395(3)	6006(2)
O(6)	10699(2)	3907(3)	8946(2)
N(1)	8347(3)	5434(3)	7229(2)
C(1)	8382(3)	8440(4)	5684(3)
C(2)	9231(3)	6550(4)	6142(3)
C(3)	9425(4)	5880(4)	4796(3)
C(8)	7084(4)	10702(4)	6555(4)
C(9)	6561(3)	5445(3)	7061(3)
C(10)	6224(3)	4121(3)	8392(3)
C(11)	4691(3)	3608(4)	8800(3)
C(12)	4762(4)	2323(4)	10150(3)
C(13)	6302(4)	1571(4)	11050(3)
C(14)	7845(4)	2087(4)	10627(3)
C(15)	7772(3)	3371(3)	9289(3)
C(16)	9154(3)	4199(3)	8553(3)

Table 2. Bond lengths (*d*) in the molecule of *meso*-**4b**

Bond	*d*/Å	Bond	*d*/Å
O(1)—C(1)	1.200(4)	C(3)—C(4)	1.526(4)
O(2)—C(1)	1.340(3)	C(9)—C(10)	1.474(4)
O(2)—C(8)	1.459(4)	C(10)—C(11)	1.390(4)
O(5)—C(9)	1.207(3)	C(10)—C(15)	1.386(4)
O(6)—C(16)	1.221(3)	C(11)—C(12)	1.390(4)
N(1)—C(2)	1.462(3)	C(12)—C(13)	1.379(4)
N(1)—C(9)	1.412(3)	C(13)—C(14)	1.403(4)
N(1)—C(16)	1.397(3)	C(14)—C(15)	1.382(4)
C(1)—C(2)	1.519(4)	C(15)—C(16)	1.486(4)
C(2)—C(3)	1.524(4)		

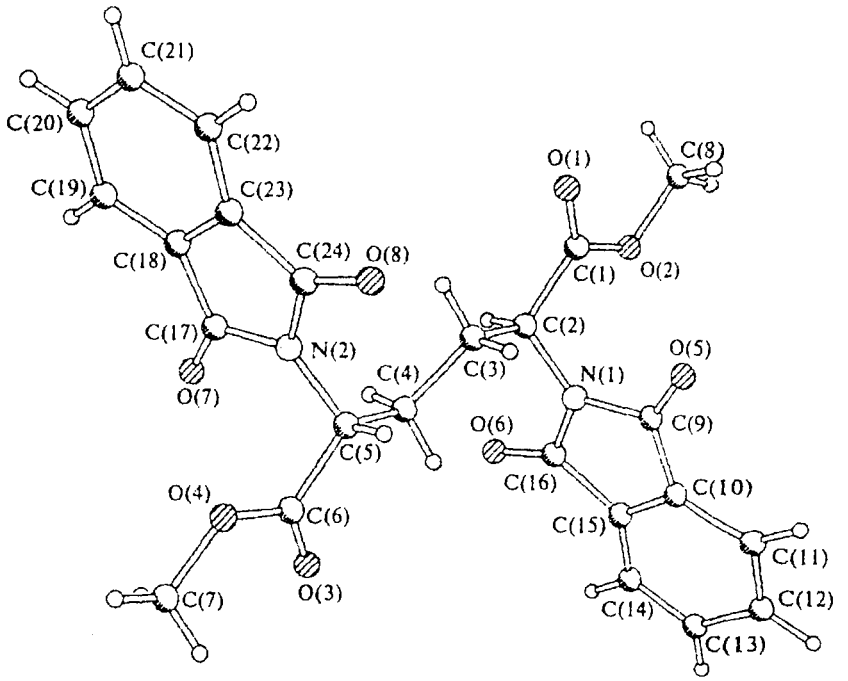


Fig. 1. The structure of the molecule of *meso*-**4b**.

Table 3. Main bond angles (ω) in the molecule of *meso*-**4b**

Angle	ω/deg	Angle	ω/deg
C(1)—O(2)—C(8)	116.3(2)	C(9)—C(10)—C(11)	130.2(3)
C(2)—N(1)—C(9)	124.2(2)	C(9)—C(10)—C(15)	108.3(2)
C(2)—N(1)—C(16)	124.6(2)	C(11)—C(10)—C(15)	121.3(2)
C(9)—N(1)—C(16)	111.1(2)	C(10)—C(11)—C(12)	117.4(3)
O(1)—C(1)—O(2)	124.4(3)	C(11)—C(12)—C(13)	121.6(3)
O(1)—C(1)—C(2)	124.1(3)	C(12)—C(13)—C(14)	120.7(3)
O(2)—C(1)—C(2)	111.3(2)	C(13)—C(14)—C(15)	117.8(3)
N(1)—C(2)—C(1)	111.1(2)	C(10)—C(15)—C(14)	121.0(3)
N(1)—C(2)—C(3)	112.4(2)	C(10)—C(15)—C(16)	108.3(2)
C(1)—C(2)—C(3)	112.0(2)	C(14)—C(15)—C(16)	130.5(3)
C(2)—C(3)—C(4)	112.7(2)	O(6)—C(16)—N(1)	124.0(2)
O(5)—C(9)—N(1)	123.7(2)	O(6)—C(16)—C(15)	129.8(2)
O(5)—C(9)—C(10)	130.1(3)	N(1)—C(16)—C(15)	106.0(2)
N(1)—C(9)—C(10)	106.1(2)		

respectively. The carbon skeleton in C(4)-derivatives of methyl *threo*-*N*-phthalylglutamate that we studied previously had a similar *trans*-*trans*-configuration.[14,15] The angle between the phthalimide fragment and the carbon chain planes is 73.5°. The O(1)—C(1)—C(2)—N—(1) and O(2)—C(1)—C(2)—N(1) torsion angles are −141.9° and 41.5°, respectively. The ester group is located in the carbon chain plane. The O(1)—C(1)—C(2)—C(3) torsion angle is −15.2°. According to the geometric parameters, the molecule of *meso*-**4b** is similar to C(4)-substituted methyl *N*-phthalylglutamates[14–17] and other derivatives of this acid.[18–20] The molecule of *meso*-**4b** has central symmetry, since the chiral centers are of opposite configurations. The crystal structure is composed of separate molecules. No contacts shorter that the sums of van der Waals radii of the corresponding atoms were observed.

Experimental

The melting points were determined on a Boetius hot-stage apparatus. The course of the reactions and the purity of individual compounds were monitored by TLC on Silufol UV-254 plates in the following solvent systems: chloroform—benzene—methanol, 12 : 10 : 1 (A); chloroform—17% ammonia—methanol, 2 : 1 : 2 (B); ethanol—concentrated ammonia, 7 : 3 (C). UV spectra were recorded on a Specord UV-VIS instrument. IR spectra were obtained on a Specord IR-75 spectrophotometer in vaseline oil. ^{1}H NMR spectra were recorded on Tesla BS-567A (100 MHz) and Bruker WH-360 (360 MHz) spectrometers with $SiMe_4$ and sodium 4,4-dimethyl-4-silapentanesulfonates as internal standards for organic solvents and D_2O, respectively. The studies of the racemization of compound **4a** and the analysis of the isomeric compositions of compounds **4a,b** were carried out by HPLC on a Milikhrom instrument with Silasorb 600 as the sorbent, a 64×3 mm column, and detection at 230 nm using the following mobile phases: hexane—2-propanol (15 : 1) for **4a** and hexane—tetrahydrofuran (5 : 1) for **4b**; the elution rate was 200 mL min^{-1}.

Methyl *threo*- and *meso*-2,4-diphthalimidoglutarates (*threo*- and *meso*-4a). A suspension of methyl 4-bromo-*N*-phthalylglutamate (**3a**)[11] (7.68 g, 20 mmol) and potassium phthalimide (6.4 g, 34.6 mmol) in DMF (35 mL) was heated for 4 h at 160 °C. The precipitate was filtered off, the DMF was distilled *in vacuo*, and $CHCl_3$ (60 mL) was added to the residue. The solution was filtered. The filtrate was washed with water, 10% NaOH, twice again with water, dried with $MgSO_4$, and concentrated; the residue was subjected to column chromatogra-

phy (150×2 cm column, silica gel L 40/100 m, system A as the eluent). The fractions with R_f 0.55 (A) were combined and concentrated *in vacuo*. The residue was crystallized from methanol and dried in a vacuum desiccator over P_2O_5 to give 2.79 g (31%) of colorless crystalline *threo*-**4a**, m.p. 181—183 °C. The retention time in HPLC was 4.8 min. UV (EtOH), λ_{max}/nm: 220, 298. IR, ν/cm^{-1}: 1740 (C=O of the ester group), 1720, 1780 (C=O of the phthalimide group). ^{1}H NMR ($CDCl_3$), δ: 3.46 (dd, 2 H, H_A(3), $H_{A'}$(3), $J_{3A,2} = J_{3A',4}$ = 9.5 Hz, $J_{3A,4} = J_{3A',2}$ = 8.0 Hz); 3.73 (s, 6 H, 2 Me); 4.71 (dd, 2 H, H(2), H(4), $J_{2,3A} = J_{4,3A'}$ = 9.5 Hz, $J_{2,3A'} = J_{4,3A}$ = 8.0 Hz); 7.79 (m, 8 H, 2 C_6H_4). Found (%): C, 61.43; H, 4.16; N, 6.27. $C_{23}H_{18}N_2O_8$. Calculated (%): C, 61.33; H, 4.03; N, 6.29.

The fractions with R_f 0.48 (A) were combined and concentrated, and the residue was crystallized from methanol and dried *in vacuo* over P_2O_5 to give 2.5 g (28%) of crystalline *meso*-**4a**, m.p. 178—180 °C. The retention time in HPLC was 7.0 min. UV (EtOH), λ_{max}/nm: 220, 298. IR, ν/cm^{-1}: 1740 (C=O of the ester group), 1720, 1780 (C=O of the phthalimide group). ^{1}H NMR ($CDCl_3$), δ: 2.85 (dt, 1 H, H_A(3), $J_{3A,3B}$ = 15.0 Hz, $J_{3A,2} = J_{3A,4}$ = 8.5 Hz); 3.45 (dt, 1 H, H_B(3), $J_{3B,3A}$ = 15.0 Hz, $J_{3B,2} = J_{3B,4}$ = 6.0 Hz); 3.76 (s, 6 H, 2 Me); 5.05 (dd, 2 H, H(2), H(4), $J_{2,3A} = J_{4,3A}$ = 8.5 Hz, $J_{2,3B} = J_{4,3B}$ = 6.0 Hz); 7.69 (m, 8 H, 2 C_6H_4). Found (%): C, 61.48; H, 4.21; N, 6.27. $C_{23}H_{18}N_2O_8$. Calculated (%): C, 61.33; H, 4.03; N, 6.29.

***threo*-2,4-Diaminoglutaric acid (*threo*-1a).** A 20% HCl solution (50 mL) was added to ***threo*-4a** (2.05 g, 4.55 mmol), and the mixture was refluxed for 9 h. The mixture was then cooled, and phthalic acid was filtered off. The hydrolysate was evaporated *in vacuo*, water was added to the residue, and the solution was again evaporated. The residue was dissolved in 85% ethanol (40 mL), the solution was cooled, and pyridine was added until precipitation ceased. The mixture was kept in a refrigerator for 3 days. The precipitate that formed was filtered off, washed with ethanol, and dried *in vacuo* to afford 0.49 g (66%) of *threo*-**1a**, dec.t. ~ 270 °C. R_f 0.30 (B). IR, ν/cm^{-1}: 1640 (C=O zwitter-ion). ^{1}H NMR (D_2O—1 *M* NaOD), δ: 1.95 (t, 2 H, 3-H_2, $J_{3,2} = J_{3,4}$ = 6.8 Hz); 3.52 (t, 2 H, H(2), H(4), $J_{2,3} = J_{4,3}$ = 6.8 Hz). Found (%): C, 37.19; H, 6.40; N, 17.16. $C_5H_{10}N_2O_4$. Calculated (%): C, 37.04; H, 6.21; N, 17.28.

***meso*-2,4-Diaminoglutaric acid (*meso*-1a)** was obtained similarly to ***threo*-1a**. Hydrolysis of ***meso*-4a** (0.66 g, 1.47 mmol) afforded 0.15 g (63%) of a colorless crystalline compound, dec.t. >270 °C. R_f 0.30 (B). IR, ν/cm^{-1}: 1640 (C=O zwitter-ion). ^{1}H NMR (^{1}H (D_2O—1 *N* NaOD), δ: 1.61 (dt, 1 H, H_A(3), $J_{3A,3B}$ = 14.5 Hz, $J_{3A,2} = J_{3A,4}$ = 8.1 Hz); 1.97 (dt, 1 H, H_B(3), $J_{3A,3B}$ = 14.5 Hz, $J_{3B,2} = J_{3B,4}$ = 6.3 Hz); 3.29 (dd, 2 H, H(2), H(4), $J_{2,3A} = J_{4,3A}$ = 8.1 Hz, $J_{2,3B} = J_{4,3B}$ = 6.3 Hz). Found (%): C, 37.06; H, 6.26; N, 16.88. $C_5H_{10}N_2O_4$. Calculated (%): C, 37.04; H, 6.21; N, 17.28.

Methyl 5-bromo-2-phthalimidoadipate (3b). 2-Phthalimidoadipic acid (**2b**) (7.26 g, 24.9 mmol), PBr_5 (34.37 g, 79.8 mmol), dry Br_2 (6.6 mL, 127.9 mmol), and a catalytic amount of I_2 were placed into a three-necked flask equipped with an effective condenser and a dropping funnel. The mixture was heated for 3.5 h at 65—67 °C under irradiation with an incandescent lamp (300 W) with periodic shaking. Then the flask was equipped with a mechanical stirrer and MeOH (35 mL) was slowly added with ice cooling and stirring. The mixture was heated for 3 h at 70 °C. The solvent was distilled off, the residual oil was dissolved in ethyl acetate. The solution was washed with a saturated solution of Na_2CO_3 and water and then dried with $MgSO_4$. The ethyl acetate was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel L 40/100 m, with hexane—benzene—dioxane, 5 : 4 : 1, as the eluent). The solvent was distilled off to afford an oily light-yellow product, R_f 0.78 (A). UV (EtOH), λ_{max}/nm: 220, 295.5. IR, ν/cm^{-1}: 1770, 1715 (C=O of the phthalimide group); 1730 (C=O of the ester group); 1613, 1600 (C=C arom.); 720 (CH arom.). ^{1}H NMR ($CDCl_3$), δ: 2.10 (m, 2 H, 4-H_2); 2.43 (m, 2 H, 3-H_2); 3.74 (s, 3 H, Me); 3.75 (s, 3 H, Me); {4.27 (t, J = 7.2 Hz), 4.30 (dd, J = 8.4, 5.9 Hz), 1 H, H(5), a mixture of *threo*- and *erythro*-diastereomers}; {4.87 (dd, J = 10.1, 5.2 Hz); 4.88 (dd, J = 10.3, 4.9 Hz), 1 H, H(2), a mixture of *threo*- and *erythro*-diastereomers}; 7.83 (m, 4 H, C_6H_4). Found (%): C, 48.63; H, 4.04; Br, 19.78; N, 3.56. $C_{16}H_{16}BrNO_6$. Calculated (%): C, 48.24; H 4.02; Br, 20.10; N, 3.52.

Methyl *meso*-2,5-diphthalimidoadipate (*meso*-4b). Potassium phthalimide (1.86 g, 10.04 mmol) was added to a solution of compound **3b** (2.0 g, 5.02 mmol) in dry DMF (15 mL), and the reaction mixture was stirred for 43 h at ~20 °C. After that, $CHCl_3$ (26 mL) and water (104 mL) were added, the product was extracted with $CHCl_3$, and the solution was washed with saturated Na_2CO_3 and water and dried with anhydrous $MgSO_4$. The solution was then concentrated *in vacuo*, and the residual oil was crystallized from EtOH to give 1.20 g (2.58 mmol) of product **4b**, m.p. 155—165 °C.

Compound **4b** (0.71 g, 1.53 mmol) was dissolved in boiling anhydrous EtOH (100 mL). The undissolved residue was filtered off and dried *in vacuo* with P_2O_5 to give 50 mg of *meso*-**4b**, m.p. 204—206 °C, R_f = 0.68 (A). The retention time in HPLC was 23.3 min. UV (EtOH), λ_{max}/nm: 220, 295.5. IR, ν/cm^{-1}: 1770, 1705 (C=O of the phthalimide group), 1745, 1715 (C=O of the ester group), 1600, 720 (arom.). ^{1}H NMR ($CDCl_3$), δ: 2.18—2.41 (m, 4 H, 2 CH_2); 3.68 (m, 6 H, 2 Me); 4.82 (m, 2 H, H(2), H(5)); 7.76—7.87 (m, 8 H, 2 C_6H_4). Found (%): C, 62.02; H, 4.53; N, 6.11. $C_{24}H_{20}N_2O_8$. Calculated (%): C, 62.06; H, 4.34; N, 6.03.

X-ray structural analysis was carried out with a single crystal of *meso*-**4b**, 0.25×0.5×0.6 mm, triclinic syngony. The unit cell parameters were: a = 7.959(5) Å, b = 8.045(3) Å, c = 9.412(4) Å, α = 73.97(3)°, β = 96.37(3)°, γ = 83.76(3)°, V = 569(1) Å^3, Z = 1; $P\bar{1}$ space group. The experiment was carried out on a RAD-4 automatic four-circle diffractometer, Mo-Kα irradiation. 1119 independent reflections with $I > 2\sigma$ (I) were obtained.

The structure was solved by the direct method using the MULTAN-CM[21] program and refined using the least-squares method in an anisotropic approximation (an isotropic approximation was used for the H atoms) to R = 0.041. The experimental weighting scheme with R_w = 0.038 was used at the final steps of refinement.

The filtrate was kept in a freezer and the precipitate that formed was filtered off and dried *in vacuo* over P_2O_5 to give 0.58 g of *threo*-**4b** containing an admixture of *meso*-**4b** with m.p. 163.5—165.5 °C. R_f 0.68 (A). The retention time in HPLC was 21.8 min (*threo*-**4b**) and 23.3 min (*meso*-**4b**). UV (EtOH), λ_{max}/nm: 220, 295.5. IR, ν/cm^{-1}: 1770, 1705 (C=O of the phthalimide group), 1745, 1715 (C=O of the ester group), 1600, 720 (arom.). ^{1}H NMR ($CDCl_3$), δ: 2.27 (m, 4 H, 2 CH_2); 3.69 (s, 6 H, 2 Me); 4.82 and 4.95 (both m, 2 H, H(2), H(5) *meso*- and *threo*-diastereomers); 7.75—7.83 (m, 8 H, 2 C_6H_4). Found (%): C, 62.15; H, 4.17; N, 6.12. $C_{24}H_{20}N_2O_8$. Calculated (%): C, 62.06; H, 4.34; N, 6.03.

2,4-Diaminoadipic acid (1b). A solution of KOH (1.37 g, 24.5 mmol) in EtOH (25 mL) was added to a suspension of compound **4b** (2.84 g, 6.12 mmol) in EtOH (50 mL), and the mixture was stirred for 5 h and concentrated *in vacuo*. The

residue was dissolved in water, and the solution was filtered. A 20% HCl solution (4 mL) was added to the filtrate and the mixture was refluxed for 14 h. The solution was cooled to ~20 °C, the precipitate was filtered off, and the filtrate was evaporated. The residue was dissolved in a minimum amount of water, the solution was filtered, and pyridine was added to pH 6—7. The precipitate was filtered off, washed with water and EtOH, and dried *in vacuo* to give 0.38 g (35.2 %) of product **1b**, dec.t. >279 °C. R_f 0.28 (C). ^{1}H NMR (DMSO-d_6), δ: 2.12 (m, 4 H, 2 CH_2); 4.76 (m, 2 H, H(2), H(5)). Found (%): C, 41.18; H, 7.15; N, 15.58. $C_6H_{12}N_2O_4$. Calculated (%): C, 40.90; H, 6.87; N, 15.90.

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